

## IN THE SPECIFICATION

Page 10, replace the paragraph starting line 21 with:

B<sup>1</sup>  
The gene Any-RF according to the present invention codes for a protein, which has an amino acid sequence: Asp-Ile-Leu-Arg-Gly (SEQ ID NO:1), which has a C-terminal amide group (SEQ ID NO:5) and which has a molecular weight of 570.959; possesses dormancy-control activity and is derived from the pre-larvae of *Antheraea yamamai*.

Page 10, replace the paragraph starting line 26 and ending in page 11, line 2, with:

B<sup>2</sup>  
The dormancy-control substance according to the present invention has an amino acid sequence: Asp-Ile-Leu-Arg-Gly (SEQ ID NO:1), has a C-terminal amide group (SEQ ID NO:5) and has a molecular weight of 570.959.

Page 12, replace the paragraph starting line 4 with:

B<sup>3</sup>  
In addition, the living cell-control agent according to the present invention, for instance, a cancer cell growth-inhibitory agent comprises, as an effective component, a peptide, which has an amino acid sequence: Asp-Ile-Leu-Arg-Gly (SEQ ID NO:1), which has a C-terminal amide group (SEQ ID NO:5) and which has a molecular weight of 570.959. This peptide is one derived from the pre-larvae of *Antheraea yamamai* as already discussed above and can be prepared by the same method used above.

Page 12, replace the paragraph starting line 11 with:

Furthermore, the living cell-control agent according to the present invention, for instance, a cancer cell growth-inhibitory agent may be one comprising, as an effective component, a peptide having an amino acid sequence: Ile-Leu-Arg-Gly (SEQ ID NO:2), which corresponds to that specified as SEQ ID NO:1 from which the N-terminal Asp residue is deleted, which has a C-terminal amide group (SEQ ID NO:6) and which has a molecular weight of 456.58.

Page 15, replace the paragraph starting on line 15 with the following paragraph:

Fig. 6 is a mass spectrometric spectrum used for determining the molecular weight of a synthetic peptide (Asp-Ile-Leu-Arg-Gly-NH<sub>2</sub>, SEQ ID ~~NO:4~~ NO:5 having the C-terminal amidated) having an amino acid sequence and C-terminal identical to those observed for the dormancy-control substance according to the present invention.

Page 16, replace the paragraph starting line 1 with:

Fig. 9 is a micrograph showing the morphological change and growth inhibition observed for rat hepatoma cells (dRLh84) when using DILRG-NH<sub>2</sub> (SEQ ID NO:5, the peptide of SEQ ID NO:1 having the C-terminal amidated) or DILRG-COOH (SEQ ID NO:1).

Page 16, replace the paragraph starting line 4 with:

Fig. 10 is a graph showing the growth-control effect of DILRG-NH<sub>2</sub> (SEQ ID NO:5, the peptide of SEQ ID NO:1 having the C-terminal amidated) or DILRG-COOH

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(SEQ ID NO:1) on the rat hepatoma cells (dRLh84) in terms of the relation between the concentration and the viable cell count.

Page 16, replace the paragraph starting line 7 with:

Fig. 11 is a graph showing the growth-control effect of DILRG-NH<sub>2</sub> (SEQ ID NO:5, the peptide of SEQ ID NO:1 having the C-terminal amidated) or PBS(-) on the rat hepatoma cells (dRLh84) in terms of the relation between the cultivation time and the viable cell count.

Page 16, replace the paragraph starting line 14 with:

Fig. 13 is a graph showing the growth-control effect of DILRG-NH<sub>2</sub> (SEQ ID NO:5, the peptide of SEQ ID NO:1 having the C-terminal amidated) on the rat hepatoma cells (dRLh84), while comparing it with those observed for other substances.

Page 17, replace the paragraph starting line 6 with:

As has been discussed above, the dormancy-control substance according to the present invention is a novel peptide having a dormancy-control function, 5 amino acid residues thereof from the N-terminal are Asp-Ile-Leu-Arg-Gly (SEQ ID NO:1), and it is a low molecular weight substance (molecular weight. 570.959) and does not have a free oxidized C-terminal, but has a C-terminal carrying an amide group (SEQ ID NO:5). This is clear from the fact that only the peptide whose C-terminal carries an amide group possesses such a control function as demonstrated by the biological assay concerning the compounds prepared in Examples as will be described below. This substance can

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be isolated and purified from, for instance, the pre-larvae of *Antheraea yamamai* or alternatively, it can be synthesized according to the conventional methods since the amino acid sequence thereof is elucidated.

Page 18, replace the paragraph starting line 3 with:

As has been discussed above, the amino acid sequence of the repressive factor of the peptide, which is involved in the maintenance of the dormancy of the pre-larvae of *Antheraea yamamai*, is Asp-Ile-Leu-Arg-Gly-NH<sub>2</sub> (SEQ ID NO:5, the peptide of SEQ ID NO:1 having the C-terminal amidated). There has not any known peptide of this type of penta-peptide even when the computer research (BLAST and FASTA) is performed and thus the penta-peptide is a novel peptide having dormancy-control activity in the biological world. This is named *Antheraea yamamai*-Repressive Factor (abbreviation: Any-RF). Nobody has ever discovered the peptide comprising 5 amino acid residues and whose C-terminal carries an amide group in the free state in the biological world till the present invention has been completed. However, the amino acid segments identical to the foregoing one: ---Asp-Ile-Leu-Arg-Gly --- can be found in the amino acid sequence of several biological proteins. For instance, the amino acid sequence is identical to that found in the putative 22.1 KD protein (193 amino acid residues) of yeast (i.e. the fragment starting from 166<sup>th</sup> to 170<sup>th</sup> amino acid residues) and that found in the precursor (202 amino acid residues) of the human leukemia-inhibitory factor (i.e. the fragment extending from 142<sup>nd</sup> to 146<sup>th</sup> amino acid residues), according to the computer research. However, the functions of the amino acid sequences of these portions have not yet been elucidated at all. In other words, the amino acid sequence in the peptide of

the present invention is sandwiched between - and C-terminals, the C-terminal has an amide group and the sequence is thus present in the free state, although the amino acid sequence of the present invention is identical to the fragment present in large protein sequences. Thus, there has never been discovered such an amino acid sequence present in the free state and possessing such a physiological function.

Page 26, please replace the paragraph starting on line 21 with the following paragraph:

The biological cell-control agent, for instance, a cancer cell growth-control agent according to the present invention comprises the penta-peptide described above as an effective component. The physiologically active substance, as the effective component, according to the present invention has an amino acid sequence comprising 5 amino acid residues from the N-terminal: Asp-Ile-Leu-Arg-Gly and whose C-terminal carries an amide group (SEQ ID NO:5), as has been discussed above. As has also been described above, the effective component can be prepared by isolating and purifying or may be prepared according to any known method using any known peptide synthesis device.

Page 36, replace the paragraph starting line 8 with:

A peptide whose primary structure was completely identical to that of the peptide isolated and purified by the foregoing procedures according to the present invention was prepared by the following method. More specifically, peptides Asp-Ile-Leu-Arg-Gly-NH<sub>2</sub> (SEQ ID NO:5, the peptide of SEQ ID NO:1 having the C-terminal amidated) (abbreviated as DILRG-NH<sub>2</sub> or RF-NH<sub>2</sub>) and Asp-Ile-Leu-Arg-Gly-COOH (SEQ ID NO:1)

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(abbreviated as DILRG-COOH or RF-COOH) were prepared according to the usual procedures using a peptide synthesizer (PSSM-8 available from Shimadzu Corporation). The purification of these peptides were carried out using a reverse phase column ULTRON VX-ODS (20mm x 250mm, available from Shinwa Kako K.K.) connected to an HPLC system (LC-10A, available from Shimadzu Corporation). The elution was carried out at a flow rate of 8 ml/min and using an acetonitrile concentration gradient (1 to 5% for 0 to 5 minutes; 5 to 60% for 5 to 35 minutes) in the presence of a 0.1% TFA to thus give active fractions. The absorbance at 220 nm was monitored. The purified peptide was mixed with an equivalent amount of a matrix (50% acetonitril/0.1% TFA saturated with  $\alpha$ -CHCA) on the sample plate, followed by drying and confirmation of the purity thereof using MALDI-TOF MS (available from Voyager PerSeptive Biosystems Company).

Page 36, replace the paragraph starting line 24 and ending page 37, line 1 with:

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Two kinds of peptides DILRG-NH<sub>2</sub> (SEQ ID NO:5, the peptide of SEQ ID NO:1 having the C-terminal amidated) (purity: not less than 95%, determined using HPLC and TOF-MS) and DILRG-COOH (SEQ ID NO:1) (purity: not less than 95%, determined using HPLC and TOF-MS) were synthesized according to the foregoing method and they were used in the following Examples.

Page 39, replace the paragraph starting on line 6 with the following paragraph:

(Example 2): Determination of Structure of Control Substance

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After dissolving, in pure water, 100 µl of the dormancy-control substance prepared in Example 1, the sequencing was carried out up to 10 cycles from the N-terminal using an aqueous solution, which contained 25 µl of the dormancy-control substance. As a result, it was confirmed that the amino acid sequence of the active substance having a dormancy-controlled activity was Asp-Ile-Leu-Arg-Gly. To examine whether the C-terminal of the active substance was in an amidated form (-NH<sub>2</sub>) or a free acid form (-COOH), this isolated and purified product and the foregoing two synthetic peptides were analyzed using MALDI-TOF MS (mass spectrometer). As a result, there were observed two large peaks at 571.858 and 572.846 for the isolated and purified product (Fig. 5), a maximum peak at 571.959 for the synthetic peptide: Asp-Ile-Leu-Arg-Gly-NH<sub>2</sub> (SEQ ID NO:5, the peptide of SEQ ID NO:1 having the C-terminal amidated) (Fig. 6) and a maximum peak at 573.045 for the synthetic peptide: Asp-Ile-Leu-Arg-Gly-COOH (SEQ ID NO:1) (Fig. 7).

Page 42, replace the paragraph starting line 5 with:

Consequently, the amino acid sequence of the repressive factor derived from *Antheraea yamamai* is Asp-Ile-Leu-Arg-Gly-NH<sub>2</sub> (SEQ ID NO:5, the peptide of SEQ ID NO:1 having the C-terminal amidated) and the molecular weight thereof can be determined by subtracting 1 (mass of a proton) from the measured value of the mass spectrometric peak or 570.959.

Page 47, replace the paragraph starting line 17 with:

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Rat hepatoma cells (dRLh84,  $3 \times 10^5$  cells) were cultured in a culture medium, to which the peptide (DILRG-NH<sub>2</sub>, SEQ ID NO:5, the peptide of SEQ ID NO:1 having the C-terminal amidated or DILRG-COOH, SEQ ID NO:1) was added in a predetermined amount (0, 50, 100, 150, 200  $\mu$ g/ml) in the presence of 5% CO<sub>2</sub> at 37°C for 40 hours. Thereafter, the culture medium was treated with trypan blue to determine the viable cell count. The results thus obtained are shown in Fig. 10.